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(54) [Title of the Invention] **Composition for Nebulizers**

(57) [Summary]

[Object] To provide a composition for nebulizers for treating acute and chronic infections of the nasal/paranasal sinuses and laryngopharynx.

[Means for Solving] Lomefloxacin and the salt thereof show broad antibacterial action, have low antigenicity, are not found to show ototoxicity, are also stable as a solution and can be made into a uniform mist, and furthermore are not affected by ultrasonic waves, so

aqueous formulations containing lomefloxacin are useful as compositions for nebulizers for treating acute or chronic infection of the nasal/paranasal sinuses and laryngopharynx.

[Claims]

[Claim 1] A composition for nebulizers that contains lomefloxacin or a salt thereof.

[Claim 2] The composition of claim 1 that is an aqueous formulation.

[Claim 3] A method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer.

[Detailed Description of the Invention]

[0001]

[Technological Field of the Invention] The present invention relates to a composition for nebulizers that contains lomefloxacin or a salt thereof. It also relates to a method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer. Here, nasal/paranasal sinuses are a general name for nasal sinuses and paranasal sinuses.

[0002]

[Prior Art] With infections of the otolaryngologic area such as nasal/paranasal sinus infections, because the shape of the nasal/paranasal sinuses is complex, with nasal drip, it is impossible to have medicine reach the entire nasal/paranasal sinuses. With infections of the laryngopharynx as well, with coating by gargling or cotton swabs, it is impossible to achieve a local dose of medicine evenly to the entire laryngopharynx. Because of this, with the otolaryngologic area, nebulizer therapy has been performed as one local chemical therapy. However, despite the fact that nebulizer therapy has been performed from a relatively long time ago, there were almost no compositions for nebulizers for the infections noted above placed on the market, and the current situation is that antibiotics,

e.g. aminoglycoside type antibiotics in injectable solution form, are dissolved and diluted using distilled water for injections. However, aminoglycoside type antibiotics have the disadvantages of having a weak antibacterial spectrum in relation to streptococcus, and being ineffective on anaerobic bacteria. Also, due to concern about ototoxicity, there is a desire for new antimicrobial nebulizer compositions.

[0003] Lomefloxacin and the salt thereof are disclosed in Unexamined Patent 60-64979, and this is a quinolone carboxylic acid type synthetic antibiotic that shows broad antibacterial action and has low antigenicity. As aqueous preparations containing the concerned antibiotic, eye drops, nose drops, and ear drops are disclosed in Unexamined Patent 63-174930, but there is no disclosure of this as a composition for nebulizers.

[0004] Meanwhile, conditions for a composition for nebulizers include (1) causing little irritation on upper respiratory tract mucous membranes, (2) having little abnormal odor or bitter taste, (3) having a broad antibacterial action, (4) having low antigenicity and being resistant to sensitization, (5) being stable as a liquid solution and not having activity lowered, (6) not being affected by ultrasonic waves with use of ultrasonic nebulizers, and (7) generating an even mist.

[0005]

[Problems the Invention Attempts to Solve] The present invention will provide a composition for nebulizers that is useful for infections of the nasal/paranasal sinuses and laryngopharynx that satisfies the conditions noted above.

[0006]

[Means for Solving the Problems] When a liquid solution containing lomefloxacin or the salt thereof was inserted in an ultrasonic inhaler (NE-U11B, OMRON Corp.) and the inhaler was operated for a set length of time, the inventors found that an even mist was generated, and the lomefloxacin or salt thereof was not affected by the ultrasonic waves.

[0007] In light of this, acute sinusitis was induced in rabbits for experimental purposes, and lomefloxacin or a salt thereof was atomized and inhaled [by the subjects], and upon study of the results of this experiment, as shown in the test examples noted below, the inventors found that a lomefloxacin mist inhalant is useful in improving symptoms of acute sinusitis in rabbits.

[0008] The present invention is based on this information, and is a preparation for nebulizers that contains lomefloxacin or a salt thereof in a composition for nebulizers. The present invention also relates to a method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer.

[0009]

[Embodiments of the Invention] The lomefloxacin used for the present invention can be produced using the method noted in Unexamined Patent 60-64979, for example. It is preferable that the lomefloxacin used in the present invention be used in a pharmacologically allowed salt form. As such a salt, we can list, for example acid-added salts including hydrochlorides, hydrosulfates, nitrate salts, hydrobromates, hydriodic acid salts, phosphates, acetates, maleates, fumarates, citrates, and tartrates, or alkali-added salts such as sodium salts, potassium salts, calcium salts, ammonium salts, or ethanol amine salts. Among these salt types, hydrochlorides are especially preferable.

[0010] It is acceptable to add as appropriate to the composition for nebulizers of the present invention additives that are normally added to items such as nose drops or mouthwash, examples of which include preservatives (p-hydroxybenzoate esters, benzalkonium chloride, chlorobutanol, etc.), chelates (sodium edetate, sodium citrate, etc.), isotonizing agents (glycerin, mannitol, sorbitol, propylene glycol, sodium chloride, etc.), buffers (carbonates, phosphates, etc.), pH adjusters (hydrochloric acid, sodium hydroxide, etc.).

[0011] It is also acceptable to blend as appropriate in the composition for nebulizers of the present invention [substances such as] mucous solvents or cellulose solvent enzyme agents that cause moisture swelling of secretions that have hardened on the upper

respiratory tract mucous membranes, reduce the surface tension thereof, and liquefy them, or [substances such as] vasoconstriction agents, mucous restoration agent, and mucous membrane lubricants. Examples of mucous dissolving agents include acetyl cystein, bromhexine hydrochloride, and surfactants (such as tyloxapol or benzalkonium chloride). Examples of cellulose solvent enzyme agents include fibrinolysin and deoxyribonuclease. Examples of vasoconstriction agents include naphazoline nitrate, tetrahydrozoline nitrate, phenylephrine hydrochloride, oxymetazoline hydrochloride, and epinephrine hydrochloride. Examples of mucous restoration agents include S-carboxymethyl cystein, and examples of mucous membrane lubricants include ambroxol hydrochloride.

[0012] The composition for nebulizers of the present invention can be used advantageously for the treatment of acute and chronic infection of the nasal/paranasal sinuses and of the laryngopharynx. Examples of such an infection include acute sinusitus, chronic sinusitus, acute virulent symptoms of chronic sinusitis, acute laryngitis, acute epiglotitis, chronic laryngitis, acute epipharyngitis, chronic epipharyngitis, acute pharyngitis, and chronic pharyngitis.

[0013] As long as the purpose of the present invention is not lost, it is possible to blend as appropriate in the composition for nebulizers of the present invention a medicinal property element other than lomefloxacin. The concentration of lomefloxacin or the salt thereof of the composition for nebulizers of the present invention differs according to things such as the degree of infection, but normally it is approximately 0.1 to 1.0 w/v %, and preferably approximately 0.3 to 1.0 w/v %, and for example when using this for an adult patient with a paranasal sinus infection, this would be used approximately once every 1 to 3 days for 1 to 2 months, and preferably approximately once a day for 1 month. When using for a laryngopharynx infection, it would be used approximately once every 1 to 2 days for 1 to 4 weeks, and preferably approximately once a day for 2 weeks.

[0014] The composition for nebulizers of the present invention can be used for both ultrasound nebulizers and compressor nebulizers.

[0015]

[Working Examples] We will explain the present invention in further detail according to the test examples and working examples below, but the present invention is not limited in any way to these.

[0016] (Test Example 1) An aqueous solution containing lomefloxacin hydrochloride was placed in an ultrasonic inhaler (NE-U11B, OMRON Corp.), and after operating this for 5, 10, 15, 20, and 25 minutes (0.75 mL/minute, knob; 5, wind velocity volume; 10 L/minute), the external appearance of each residual fluid was observed, and when the pH and decomposition products of lomefloxacin were measured, a change in the external appearance and pH was found for the residual fluids. Also, no decomposition products of lomefloxacin were detected from the residual fluids. From this fact, it was determined that with ultrasonic type nebulizers, lomefloxacin is not affected by ultrasonic waves.

[0017] (Test Example 2) The composition of test example 2 to be described hereafter was placed in an ultrasonic inhaler (NE-U11B, OMRON Corp.), it was operated under the conditions noted above, and using an Anderson sampler (AN-200 model, Shibata Scientific Technology, Ltd.), when the particle diameter of the generated mist was measured, the average value was 3.815 μm, which was in the range of mist radius that can be suitably used for a nebulizer (approximately 1 to 20 μm).

[0018] (Test Example 3) Effect On Acute Sinusitis in Rabbits

(Experimental Method) We used white male rabbits of weight approximately 2 kg with no nasal disorders for macroscopic observation. To produce an acute sinusitis model, we followed the method of Kawahori, et al (Otolaryngology, Volume 59, pages 289 to 293, 1987). Specifically, 1 mL of a bacterial suspension of staphylococcus aureus clinical isolate (10^8 CFU/mL) was continuously injected into both maxillary sinuses of the rabbits once a day for 3 days, to induce acute sinusitis. From the day after the bacterial injection of the third day, a homemade nose nozzle was inserted into both sinuses of the rabbits, and a solution dissolved using a base (glycerin 2.6 w/v %, sodium edetate 0.01 w/v %, benzalkonium chloride 0.002 w/v %, a suitable volume of sterilized purified water, and sodium hydroxide were used to adjust to pH 5.5) to achieve lomefloxacin hydrochloride of 0.1, 0.3, and 0.5 w/v % was atomized for inhalation continuously for 7 days for 5 minutes at a time using 2 mL twice a day using an ultrasonic inhaler (NE-U11B,

OMRON Corp.). After killing the rabbits under anesthesia the day after ending the drug dosing, the maxillary sinus was extricated and a Seed Swab (Eiken Industries Co., Ltd.) was used to sample the secretions on the mucous membrane, a bacteria test was performed with this as a bacterial test sample, and the positive rate was calculated. A judgment was also made according to the grading criterion noted below on the volume of residual fluid in the maxillary sinus and on the state of the mucous membrane. Note that a saline solution atomization inhalation was performed in the same manner on a control group.

[0019] Criterion for Grading the State of the Pooled Fluid and Mucous Membrane Within the Maxillary Sinus

1. Pooled Fluid

Findings	Points
None	0
Slight amount of pooled fluid in sinus found	1.0
Purulent pooled fluid found in 1/4 of maxillary sinus	2.0
Purulent pooled fluid found in 1/2 of maxillary sinus	3.0
Purulent pooled fluid found in more than 3/4 of maxillary sinus	4.0

2. Mucous Membrane Color Tone

Color Tone	Points
Normal	0
Slightly Red	0.5
Red	1.0
Dark Red	2.0
Pale	3.0

3. Mucous Membrane Swelling

Findings	Points
None	0
Slight amount of swelling found	0.5
Light swelling found	1.0
Clear swelling found to occupy 1/4 of maxillary sinus	2.0
Clear swelling found to occupy 1/2 of maxillary sinus	3.0
Clear swelling found to occupy more than 3/4 of maxillary sinus	4.0

[0020] (Experiment Results) As shown in table 1, atomization inhalation of lomefloxacin was effective on acute sinusitis in rabbits.

[0021]

[Table 1]

Pharmacological Agent	Number of Examples	Germ Test Positive Rate (%)	Condition in Maxillary Sinus		
			Pooled Fluid	Mucous Membrane Color Tone	Mucous Membrane Swelling
Saline Solution	6	66.7	1.5 ± 0.3	1.8 ± 0.6	1.2 ± 0.2
0.1 w/v % Lomefloxacin	8	50.0	1.3 ± 0.3	0.6 ± 0.1	0.7 ± 0.1
0.3 w/v % Lomefloxacin	10	60.0	1.0 ± 0.0	0.6 ± 0.1	0.5 ± 0.0*
0.5 w/v % Lomefloxacin	10	40.0	0.6 ±0.2	0.6 ± 0.1	0.4 ± 0.1 **

Values indicate the average value ± the standard deviation.

*: Indicates that there is a significant difference when there is a significance level of less than 0.05 % in relation to the saline solution dosing group.

**: Indicates there is a significant difference when there is a significance level of less than [illegible; text covered over in copy] % in relation to the saline solution dosing group.

[0022] (Test Example 4) Migration Test of Lomefloxacin [illegible; text covered over in copy]

(Experimental Method) A Japanese white male rabbit was retained in a retention container, and underwent atomization inhalation with an ultrasonic inhaler (NE-U11B, OMRON Corp.) for 5 minutes once a day using 2 mL of the composition of working example 2 to be described later. Rabbits were killed at 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after atomization inhalation, the nasal cavity was extricated, and the mucous membranes of the left and right maxillary sinus were collected. Blood was collected from the ear vein over a period of time, and serum was isolated after centrifuging. The lomefloxacin in the collected mucous membranes and serum was measured by HPLC.

[0023] (Experiment Results) Table 2 shows the transition in tissue concentration of the lomefloxacin in the maxillary sinus mucous membranes and serum.

[0024]

[Table 2]

Time	Lomefloxacin Migration Volume	
	Maxillary Sinus (μg/g tissue concentration volume)	Serum (μg/mL)
After 15 minutes	12.69 ± 7.61	0.047 ± 0.019
After 30 minutes	3.93 ± 1.52	0.075 ± 0.024
After 1 hour	1.69 ± 0.37	0.062 ± 0.020
After 2 hours	1.11 ± 0.48	0.051 ± 0.018
After 4 hours	0.74 ± 0.21	0.033 ± 0.020 a)

Values indicate the average value ± the standard deviation. (The example count was 5 examples each, but a) was 3 examples.)

[0025] Lomefloxacin migrates in high concentration to the maxillary sinus mucous membranes which are the target site, but there is only slight migration to the serum, and we found that it can be used safely without having a systemic effect.

[0026] (Test Example 5) Lomefloxacin Toxicity Test When Used With a Nebulizer

2 mL of the composition of working example 2 to be described later was used in an ultrasonic inhaler (NE-U11B, OMRON Corp.) on rabbits, and inhalation was continued for 42 days for 5 minutes once a day, and when we studied toxicity, there were no cases of death during the period the nebulizer was used, and no abnormalities were found in the general condition, weight, food consumption, macroscopic observation of each organ, or wet weight of the organs. Also, with the histopathological evaluation of the respiratory organs (middle meatus, paranasal sinuses (maxillary sinus), pharynx (including the tonsils), laryngopharynx, trachea, lungs, and tracheal lymph nodes), there was a finding of slight cell wetness into the lung lymph nodes and into the pulmonary alveoli, but the same findings were acknowledged for the saline solution dosing group, so there was no difference. Specifically, it was judged that there was no irritation or toxicity even when lomefloxacin hydrochloride was used for 6 weeks in the form of nebulizer therapy.

[0027] (Test Example 6) Lomefloxacin Ototoxicity Test

0.2 mL of the composition of working example 2 to be described later was injected once in the middle ear of the left ear of a marmot, and this was done twice each day at 8 hour intervals for 14 days, and we studied the effect on the ear tissues, but no difference was found in the left and right ear for the auditory brainstem response threshold in terms of acoustic sensory function, and histopathologically as well, no abnormalities were found in the vestibular organs, cochlear canal, or middle ear mucous membranes, so it was determined that lomefloxacin is not ototoxic.

[0028] (Working Examples)

Working Example 1: The formula below was mixed, pH was adjusted to 6.5 using sodium hydroxide, and this was used as a composition for nebulizers.

Lomefloxacin hydrochloride	0.3 g
Sodium hydroxide	Suitable amount

Saline solution	Total volume 100 mL

[0029]

Working Example 2: The formula noted below was mixed, pH was adjusted to 5.5 using sodium hydroxide, and this was used as a composition for nebulizers.

Lomefloxacin hydrochloride	0.5 g
Glycerin	2.6 g
Sodium edetate	0.01 g
Benzalkonium chloride	0.002 g
Sodium hydroxide	Suitable amount
Saline solution	Total volume 100 mL (pH 5.5)

[0030]

Working Example 3: The glycerin in the formula of working example 2 was substituted with mannitol (5.1 g), propylene glycol (2.0 g), D-sorbitol (5.48 g), or glucose (5.51 g), and a composition for nebulizers was prepared.

[0031]

[Merits of the Invention] The lomefloxacin and salt thereof used with the present invention has a broad antibacterial action, has low antigenicity, and is not found to be ototoxic, and is also stable as a liquid solution and can be made into an even mist, and furthermore is not affected by ultrasonic waves, so it can be safely and effectively used for nebulizer therapy for treating acute and chronic infections of the nasal/paranasal sinuses and laryngopharynx.

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(54)【発明の名称】　ネプライザー用組成物

(57)【要約】

【課題】　鼻・副鼻腔および咽喉頭の急性および慢性の感染症の治療のためのネプライザー用組成物を提供することにある。

【解決手段】　ロメフロキサシンおよびその塩は、抗菌活性が広く、抗原性が低く、かつ耳毒性が認められず、また、溶液として安定で、均一なミスト化が可能で、さらに超音波の影響を受けないため、ロメフロキサシンを含有してなる水性液剤は、鼻・副鼻腔および咽喉頭の急性および慢性の感染症の治療のためのネプライザー用組成物として有用である。

【特許請求の範囲】
【請求項１】ロメフロキサシンまたはその塩を含有してなるネブライザー用組成物。
【請求項２】水性液剤である請求項１記載の組成物。
【請求項３】ロメフロキサシンまたはその塩を含有する水性液剤を、鼻・副鼻腔、咽頭および喉頭等の上気道部位にネブライザーを用いて噴霧吸入する方法。
【発明の詳細な説明】
【０００１】
【発明の属する技術分野】本発明は、ロメフロキサシンまたはその塩を含有してなるネブライザー用組成物に関する。また、本発明はロメフロキサシンまたはその塩を含有する水性液剤を、鼻・副鼻腔、咽頭および喉頭等の上気道部位にネブライザーを用いて噴霧吸入する方法に関する。ここで鼻・副鼻腔とは、鼻腔および副鼻腔を総称したものをいう。
【０００２】
【従来の技術】耳鼻咽喉科領域の感染症、例えば鼻・副鼻腔感染症では、鼻・副鼻腔の形態が複雑であるため、点鼻では鼻・副鼻腔全体に薬物を到達させることが不可能である。また、咽喉頭感染症の場合においても、うがいや綿棒による塗布では、咽喉頭の全域に一様に薬物を局所投与することは不可能である。そのため、耳鼻咽喉科領域では、局所的化学療法の一つとしてネブライザー療法が行なわれてきた。しかし、比較的古くからネブライザー療法が行なわれてきているにもかかわらず、上記感染症のためのネブライザー用の組成物はほとんど上市されておらず、抗生物質、例えばアミノグリコシド系抗生物質の注射剤などが注射用蒸留水で溶解、希釈して使用されているのが現状である。しかし、アミノグリコシド系抗生物質は、連鎖球菌に対する抗菌力が弱く、嫌気性菌に無効であるなどの欠点がある。また、耳毒性も懸念されていることから、新しい抗菌薬のネブライザー用組成物が所望されている。
【０００３】ロメフロキサシンまたはその塩は特開昭６０－６４９７９に開示されており、抗菌活性が広く、かつ抗原性の低いキノロンカルボン酸系の合成抗菌剤である。当該抗菌剤を含有する水性製剤としては、点眼剤、点鼻剤および点耳剤が特開昭６３－１７４９３０に開示されているが、ネブライザー用組成物としての開示はみられない。
【０００４】一方、ネブライザー用組成物は、（１）上気道粘膜への刺激性が少なく、（２）異臭および苦味が少なく、（３）抗菌活性が広く、かつ（４）抗原性が低く感作しにくく、（５）溶液として安定で、活性が低下せず、（６）超音波式ネブライザーに使用するためには超音波の影響を受けず、（７）均一なミストを生じることなどが条件となる。
【０００５】
【発明が解決しようとする課題】本発明は、上記の条件を満たす鼻・副鼻腔および咽喉頭の感染症に有用なネブライザー用組成物を提供することである。
【０００６】
【課題を解決するための手段】本発明者は、ロメフロキサシンまたはその塩を含有する溶液を超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）に入れ、一定時間作動させたところ、均一なミストが発生し、さらに、超音波によりロメフロキサシンまたはその塩は影響を受けないことを知った。
【０００７】そこで、実験的にウサギに急性副鼻腔炎を誘発し、ロメフロキサシンまたはその塩を噴霧吸入させ、その効果を検討したところ、下記試験例に示したようにロメフロキサシンの噴霧吸入はウサギの急性副鼻腔炎症状を改善するのに有用であることを知った。
【０００８】本発明はこれらの知見に基づくもので、ネブライザー用組成物中にロメフロキサシンまたはその塩を含有してなるネブライザー用製剤である。また、本発明はロメフロキサシンまたはその塩を含有する水性液剤を、鼻・副鼻腔、咽頭および喉頭等の上気道部位にネブライザーを用いて噴霧吸入する方法に関するものである。
【０００９】
【発明の実施の形態】本発明に使用されるロメフロキサシンは、例えば特開昭６０－６４９７９に記載された方法で製造することができる。本発明に使用されるロメフロキサシンは、薬理学的に許容される塩の形態で使用するのが好ましい。該塩としては、たとえば塩酸塩、硫酸塩、硝酸塩、臭化水素酸塩、ヨウ化水素酸塩、リン酸塩、酢酸塩、マレイン酸塩、フマール酸塩、クエン酸塩および酒石酸塩などの酸付加塩、またはナトリウム塩、カリウム塩、カルシウム塩、アンモニウム塩、エタノールアミン塩などのアルカリ付加塩などが挙げられる。これら塩類の中でも、とりわけ塩酸塩が好ましい。
【００１０】本発明のネブライザー用組成物は、点鼻剤やうがい薬などに通常用いられる添加剤、例えば保存剤（パラオキシ安息香酸エステル類、塩化ベンザルコニウム、塩化ベンゼトニウム、クロロブタノールなど）、キレート剤（エデト酸ナトリウム、クエン酸ナトリウムなど）、等張化剤（グリセリン、マンニトール、ソルビトール、プロピレングリコール、塩化ナトリウムなど）、緩衝剤（炭酸塩、リン酸塩など）、ｐＨ調整剤（塩酸、水酸化ナトリウムなど）などを適宜添加してもよい。
【００１１】また、本発明のネブライザー用組成物には、上気道粘膜に固着した分泌物に対し、これを湿潤膨化させ、その表面張力を低下させ、さらに液化する粘液溶解剤や繊維素溶解酵素剤、また、血管収縮剤、粘液修復剤および粘膜潤滑剤などを適宜配合してもよい。粘液溶解剤としては、例えばアセチルシステイン、塩酸ブロムヘキシン、界面活性剤（チロキサポール、塩化ベンザルコニウムなど）などが挙げられる。繊維素溶解酵素剤

としては、例えばフィブリノリジン、デオキシリボヌクレアーゼなどが挙げられる。血管収縮剤としては、硝酸ナファゾリン、硝酸テトラハイドロゾリン、塩酸フェニレフリン、塩酸オキシメタゾリン、塩酸エピネフリンなどが挙げられる。粘液修復剤としてはＳ－カルボキシメチルシステインなどが挙げられ、粘膜潤滑剤としては塩酸アンブロキソールなどが挙げられる。

【００１２】本発明のネブライザー用組成物は、鼻・副鼻腔、咽喉頭の急性および慢性の感染症の治療に有利に使用することができる。該感染症としては、たとえば急性副鼻腔炎、慢性副鼻腔炎、慢性副鼻腔炎急性憎悪症、急性喉頭炎、急性喉頭蓋炎、慢性喉頭炎、急性上咽頭炎、慢性上咽頭炎、急性咽頭炎および慢性咽頭炎などが挙げられる。

【００１３】本発明のネブライザー用組成物には、本発明の目的を損なわない限り、ロメフロキサシン以外の薬効成分を適宜配合することもできる。本発明のネブライザー用組成物のロメフロキサシンまたはその塩の濃度は、感染症の程度などによっても異なるが、通常０．１～１．０ｗ／ｖ％程度、好ましくは０．３～１．０ｗ／ｖ％程度とし、例えば、成人の副鼻腔感染症の患者に用いる場合には、１～３日に１回、１～２月程度、好ましくは１日１回１月程度である。咽喉頭感染症に用いる場合、１～２日に１回、１～４週程度、好ましくは１日１回２週間程度である。

【００１４】本発明のネブライザー用組成物は超音波式ネブライザーおよびコンプレッサー式ネブライザーのいずれにも使用することができる。

【００１５】

【実施例】本発明を以下の試験例および実施例に従いさらに詳細に説明するが、本発明はこれらによりなんら限定されるものではない。

【００１６】〔試験例１〕塩酸ロメフロキサシンを含有する水溶液を超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）に入れ、５、１０、１５、２０および２５分間、作動（０．７５ｍＬ／分、ツマミ；５、風速弱；１０Ｌ／分）させた後、各残液の外観観察、ｐＨおよびロメフロキサシンの分解物の測定を行なったところ、各残液は、外観およびｐＨの変化を認めなかった。また、各残液から、ロメフロキサシンの分解物は検出されなかった。このことから、ロメフロキサシンは超音波型ネブライザーにおいて、超音波の影響を受けないことが判った。

【００１７】〔試験例２〕後記実施例２の組成物を超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）に入れ、上記条件下で作動させ、アンダーセンサンプラー（ＡＮ－２００型，柴田科学器械工業株式会社製）を用い、発生したミストの粒子径の測定を行ったところ、その平均値は３．８１８μｍで、ネブライザーとして適用できるミスト径の範囲内（約１～２０μｍ）であった。

【００１８】〔試験例３〕ウサギの急性副鼻腔炎に対する作用

（実験方法）肉眼観察にて鼻疾患のない体重約２ｋｇの白色雄性ウサギを用いた。急性副鼻腔炎モデルの作製は川堀らの方法（耳鼻咽喉科，５９巻，２８９～２９３頁，１９８７年）に準じて行なった。すなわち、スタフィロコックス　アウレウス臨床分離株の懸濁菌液１ｍＬ（10^8 ＣＦＵ／ｍＬ）をウサギの両側上顎洞内に１日１回３日間連続注入し、急性副鼻腔炎を発症させた。３回目の菌注入の翌日よりウサギの両鼻腔に自家製の鼻ノズルを挿入し、塩酸ロメフロキサシンを０．１、０．３および０．５ｗ／ｖ％となるよう基剤（グリセリン２．６ｗ／ｖ％，エデト酸ナトリウム０．０１ｗ／ｖ％，塩化ベンザルコニウム０．００２ｗ／ｖ％，滅菌精製水適量，水酸化ナトリウムでｐＨを５．５に調整）で溶解した溶液を超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）を用いて１日２回２ｍＬを５分間かけて７日間連続噴霧吸入させた。薬物投与終了翌日にウサギを麻酔死させた後、上顎洞を開放し粘膜上の分泌物をシードスワブ（エイケン社製）で採取し、菌検査用試料とし菌検査を行って陽性率を算出した。また、上顎洞内の貯留液の量および粘膜の状態を下記の採点基準に従い判定した。なお、対照群には生理食塩液を同様に噴霧吸入させた。

【００１９】

上顎洞内の貯留液および粘膜の状態の採点基準

１．貯留液：

所　　見	点
なし	０
僅かに膿性貯留液が認められる	１．０
上顎洞の１／４に膿性貯留液が認められる	２．０
上顎洞の１／２に膿性貯留液が認められる	３．０
上顎洞の３／４以上に膿性貯留液が認められる	４．０

２．粘膜の色調：

色　調	点
正常	０
薄赤	０．５
赤	１．０

濃赤　　２．０
蒼白　　３．０

３．粘膜の腫脹：

所見	点
なし	０
僅かに腫脹が認められる	０．５
軽度の腫脹が認められる	１．０
上顎洞の１／４を占める明らかな腫脹が認められる	２．０
上顎洞の１／２を占める明らかな腫脹が認められる	３．０
上顎洞の３／４以上を占める明らかな腫脹が認められる	４．０

【００２０】（実験結果）表１に示したように、ロメフロキサシンの噴霧吸入はウサギの急性副鼻腔炎に有効であった。

【００２１】
【表１】

薬物	例数	菌検査陽性率 (%)	上顎洞内の状態		
			貯留液	粘膜の色調	粘膜の腫脹
生理食塩液	6	66.7	1.5±0.3	1.8±0.6	1.2±0.2
0.1w/v% ロメフロキサシン	8	50.0	1.3±0.3	0.6±0.1	0.7±0.1
0.3w/v% ロメフロキサシン	10	60.0	1.0±0.0	0.6±0.1	0.5±0.0*
0.5w/v% ロメフロキサシン	10	40.0	0.6±0.2	0.6±0.1	0.4±0.1**

値は平均値±標準誤差を示す。
* ：生理食塩液投与群に対し、0.05%未満の危険率で有意差のあることを示す。
** ：生理食塩液投与群に対し、0.01%未満の危険率で有意差のあることを示す。

【００２２】〔試験例４〕：ロメフロキサシンの移行性試験
（実験方法）日本白色種雄性ウサギを保定缶に保定し、後記実施例２の組成物を１日１回２ｍＬを５分間、超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）で噴霧吸入した。噴霧吸入後１５、３０分、１、２および４時間後に屠殺し、鼻腔を開放し、左右の上顎洞粘膜を採取した。また、経時的に耳静脈より血液を採取し、遠心分離後血清を分取した。採取した粘膜および血清中のロメフロキサシンをＨＰＬＣで測定した。

【００２３】（実験結果）上顎洞粘膜および血清中のロメフロキサシンの組織濃度の推移を表２に示した。

【００２４】
【表２】

時間	ロメフロキサシン移行量	
	上顎洞(μg/g組織湿重量)	血清（μg／mL）
１５分後	12.69±7.61	0.047±0.019
３０分後	3.93±1.52	0.075±0.024
１時間後	1.69±0.37	0.062±0.020
２時間後	1.11±0.48	0.051±0.018
４時間後	0.74±0.21	0.033±0.020[a)]

値は平均値±標準誤差を示す〔例数は各５例（ただし、a)は３例）〕。

【００２５】ロメフロキサシンは、対象部位である上顎洞粘膜には高濃度で移行するが、血清への移行は僅かで、全身的に影響をおよぼさず、安全に使用できることが判った。

【００２６】〔試験例５〕ネブライザー使用時におけるロメフロキサシンの毒性試験
ウサギに後記実施例２の組成物を超音波式吸入器（ＮＥ－Ｕ１１Ｂ，オムロン社製）を用いて、１日１回２ｍＬを５分間かけて、４２日間連続吸入させ、毒性について検討したところ、ネブライザー使用期間中の死亡例はなく、一般状態、体重、摂餌量、各臓器の肉眼観察、臓器湿重量にも異常は認められなかった。また、呼吸器官〔中鼻道、副鼻腔（上顎洞）、咽頭（扁桃を含む）、咽喉、気管、肺、気管リンパ節〕の病理組織評価では、肺リンパ節、肺胞内へのごく軽度の細胞湿潤の所見が認められたが、生理食塩液投与群にも同等の所見が認めら

れ、差は無かった。すなわち、塩酸ロメフロキサシンを６週間、ネブライザー療法に使用しても刺激や毒性のないことが判った。

【００２７】〔試験例６〕ロメフロキサシンの耳毒性試験

モルモットの左耳に後記実施例２の組成物を１回０．２ｍＬ、８時間間隔で１日２回、１４日間中耳腔内に注入し、耳組織に及ぼす影響を検討したが、聴覚機能において聴性脳幹反応閾値に左右耳で差は認められず、また、組織学的にも前庭器、蝸牛、中耳粘膜に異常が認められなかったことから、ロメフロキサシンには耳毒性がないことが判った。

【００２８】〔実施例〕

実施例１．下記処方を混合し、水酸化ナトリウムでｐＨを６．５に調整してネブライザー用組成物とした。

塩酸ロメフロキサシン	０．３　ｇ
水酸化ナトリウム	適量
生理食塩液	全量１００ｍＬ

とした。

【００２９】実施例２．下記処方を混合し、水酸化ナトリウムでｐＨを５．５に調整してネブライザー用組成物

塩酸ロメフロキサシン	０．５　ｇ
グリセリン	２．６　ｇ
エデト酸ナトリウム	０．０１ｇ
塩化ベンザルコニウム	０．００２ｇ
水酸化ナトリウム	適量
滅菌精製水	全量１００ｍＬ
	（ｐＨ５．５）

【００３０】実施例３．実施例２の処方のグリセリンを、マンニトール（５．１ｇ）、プロピレングリコール（２．０ｇ）、Ｄ－ソルビトール（５．４８ｇ）またはブドウ糖（５．５１ｇ）に置換し、ネブライザー用組成物を調製した。

【００３１】【発明の効果】本発明で使用されるロメフロキサシンまたはその塩は、抗菌活性が広く、抗原性が低く、かつ耳毒性が認められず、また、溶液として安定で、均一なミスト化が可能で、さらに超音波の影響を受けないため、安全に、鼻・副鼻腔、咽喉頭の急性および慢性の感染症の治療のためのネブライザー療法に有利に利用できる。

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(54) [Title of the Invention] **Composition for Nebulizers**

(57) [Summary]

[Object] To provide a composition for nebulizers for treating acute and chronic infections of the nasal/paranasal sinuses and laryngopharynx.

[Means for Solving] Lomefloxacin and the salt thereof show broad antibacterial action, have low antigenicity, are not found to show ototoxicity, are also stable as a solution and can be made into a uniform mist, and furthermore are not affected by ultrasonic waves, so

aqueous formulations containing lomefloxacin are useful as compositions for nebulizers for treating acute or chronic infection of the nasal/paranasal sinuses and laryngopharynx.

[Claims]

[Claim 1] A composition for nebulizers that contains lomefloxacin or a salt thereof.

[Claim 2] The composition of claim 1 that is an aqueous formulation.

[Claim 3] A method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer.

[Detailed Description of the Invention]

[0001]

[Technological Field of the Invention] The present invention relates to a composition for nebulizers that contains lomefloxacin or a salt thereof. It also relates to a method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer. Here, nasal/paranasal sinuses are a general name for nasal sinuses and paranasal sinuses.

[0002]

[Prior Art] With infections of the otolaryngologic area such as nasal/paranasal sinus infections, because the shape of the nasal/paranasal sinuses is complex, with nasal drip, it is impossible to have medicine reach the entire nasal/paranasal sinuses. With infections of the laryngopharynx as well, with coating by gargling or cotton swabs, it is impossible to achieve a local dose of medicine evenly to the entire laryngopharynx. Because of this, with the otolaryngologic area, nebulizer therapy has been performed as one local chemical therapy. However, despite the fact that nebulizer therapy has been performed from a relatively long time ago, there were almost no compositions for nebulizers for the infections noted above placed on the market, and the current situation is that antibiotics,

e.g. aminoglycoside type antibiotics in injectable solution form, are dissolved and diluted using distilled water for injections. However, aminoglycoside type antibiotics have the disadvantages of having a weak antibacterial spectrum in relation to streptococcus, and being ineffective on anaerobic bacteria. Also, due to concern about ototoxicity, there is a desire for new antimicrobial nebulizer compositions.

[0003] Lomefloxacin and the salt thereof are disclosed in Unexamined Patent 60-64979, and this is a quinolone carboxylic acid type synthetic antibiotic that shows broad antibacterial action and has low antigenicity. As aqueous preparations containing the concerned antibiotic, eye drops, nose drops, and ear drops are disclosed in Unexamined Patent 63-174930, but there is no disclosure of this as a composition for nebulizers.

[0004] Meanwhile, conditions for a composition for nebulizers include (1) causing little irritation on upper respiratory tract mucous membranes, (2) having little abnormal odor or bitter taste, (3) having a broad antibacterial action, (4) having low antigenicity and being resistant to sensitization, (5) being stable as a liquid solution and not having activity lowered, (6) not being affected by ultrasonic waves with use of ultrasonic nebulizers, and (7) generating an even mist.

[0005]

[Problems the Invention Attempts to Solve] The present invention will provide a composition for nebulizers that is useful for infections of the nasal/paranasal sinuses and laryngopharynx that satisfies the conditions noted above.

[0006]

[Means for Solving the Problems] When a liquid solution containing lomefloxacin or the salt thereof was inserted in an ultrasonic inhaler (NE-U11B, OMRON Corp.) and the inhaler was operated for a set length of time, the inventors found that an even mist was generated, and the lomefloxacin or salt thereof was not affected by the ultrasonic waves.

[0007] In light of this, acute sinusitis was induced in rabbits for experimental purposes, and lomefloxacin or a salt thereof was atomized and inhaled [by the subjects], and upon study of the results of this experiment, as shown in the test examples noted below, the inventors found that a lomefloxacin mist inhalant is useful in improving symptoms of acute sinusitis in rabbits.

[0008] The present invention is based on this information, and is a preparation for nebulizers that contains lomefloxacin or a salt thereof in a composition for nebulizers. The present invention also relates to a method of doing atomized inhalation of an aqueous formulation that contains lomefloxacin or a salt thereof in an upper respiratory tract site such as the nasal/paranasal sinuses, pharynx, or larynx using a nebulizer.

[0009]

[Embodiments of the Invention] The lomefloxacin used for the present invention can be produced using the method noted in Unexamined Patent 60-64979, for example. It is preferable that the lomefloxacin used in the present invention be used in a pharmacologically allowed salt form. As such a salt, we can list, for example acid-added salts including hydrochlorides, hydrosulfates, nitrate salts, hydrobromates, hydriodic acid salts, phosphates, acetates, maleates, fumarates, citrates, and tartrates, or alkali-added salts such as sodium salts, potassium salts, calcium salts, ammonium salts, or ethanol amine salts. Among these salt types, hydrochlorides are especially preferable.

[0010] It is acceptable to add as appropriate to the composition for nebulizers of the present invention additives that are normally added to items such as nose drops or mouthwash, examples of which include preservatives (p-hydroxybenzoate esters, benzalkonium chloride, chlorobutanol, etc.), chelates (sodium edetate, sodium citrate, etc.), isotonizing agents (glycerin, mannitol, sorbitol, propylene glycol, sodium chloride, etc.), buffers (carbonates, phosphates, etc.), pH adjusters (hydrochloric acid, sodium hydroxide, etc.).

[0011] It is also acceptable to blend as appropriate in the composition for nebulizers of the present invention [substances such as] mucous solvents or cellulose solvent enzyme agents that cause moisture swelling of secretions that have hardened on the upper

respiratory tract mucous membranes, reduce the surface tension thereof, and liquefy them, or [substances such as] vasoconstriction agents, mucous restoration agent, and mucous membrane lubricants. Examples of mucous dissolving agents include acetyl cystein, bromhexine hydrochloride, and surfactants (such as tyloxapol or benzalkonium chloride). Examples of cellulose solvent enzyme agents include fibrinolysin and deoxyribonuclease. Examples of vasoconstriction agents include naphazoline nitrate, tetrahydrozoline nitrate, phenylephrine hydrochloride, oxymetazoline hydrochloride, and epinephrine hydrochloride. Examples of mucous restoration agents include S-carboxymethyl cystein, and examples of mucous membrane lubricants include ambroxol hydrochloride.

[0012] The composition for nebulizers of the present invention can be used advantageously for the treatment of acute and chronic infection of the nasal/paranasal sinuses and of the laryngopharynx. Examples of such an infection include acute sinusitus, chronic sinusitus, acute virulent symptoms of chronic sinusitis, acute laryngitis, acute epiglotitis, chronic laryngitis, acute epipharyngitis, chronic epipharyngitis, acute pharyngitis, and chronic pharyngitis.

[0013] As long as the purpose of the present invention is not lost, it is possible to blend as appropriate in the composition for nebulizers of the present invention a medicinal property element other than lomefloxacin. The concentration of lomefloxacin or the salt thereof of the composition for nebulizers of the present invention differs according to things such as the degree of infection, but normally it is approximately 0.1 to 1.0 w/v %, and preferably approximately 0.3 to 1.0 w/v %, and for example when using this for an adult patient with a paranasal sinus infection, this would be used approximately once every 1 to 3 days for 1 to 2 months, and preferably approximately once a day for 1 month. When using for a laryngopharynx infection, it would be used approximately once every 1 to 2 days for 1 to 4 weeks, and preferably approximately once a day for 2 weeks.

[0014] The composition for nebulizers of the present invention can be used for both ultrasound nebulizers and compressor nebulizers.

[0015]

[Working Examples] We will explain the present invention in further detail according to the test examples and working examples below, but the present invention is not limited in any way to these.

[0016] (Test Example 1) An aqueous solution containing lomefloxacin hydrochloride was placed in an ultrasonic inhaler (NE-U11B, OMRON Corp.), and after operating this for 5, 10, 15, 20, and 25 minutes (0.75 mL/minute, knob; 5, wind velocity volume; 10 L/minute), the external appearance of each residual fluid was observed, and when the pH and decomposition products of lomefloxacin were measured, a change in the external appearance and pH was found for the residual fluids. Also, no decomposition products of lomefloxacin were detected from the residual fluids. From this fact, it was determined that with ultrasonic type nebulizers, lomefloxacin is not affected by ultrasonic waves.

[0017] (Test Example 2) The composition of test example 2 to be described hereafter was placed in an ultrasonic inhaler (NE-U11B, OMRON Corp.), it was operated under the conditions noted above, and using an Anderson sampler (AN-200 model, Shibata Scientific Technology, Ltd.), when the particle diameter of the generated mist was measured, the average value was 3.815 μm, which was in the range of mist radius that can be suitably used for a nebulizer (approximately 1 to 20 μm).

[0018] (Test Example 3) Effect On Acute Sinusitis in Rabbits

(Experimental Method) We used white male rabbits of weight approximately 2 kg with no nasal disorders for macroscopic observation. To produce an acute sinusitis model, we followed the method of Kawahori, et al (Otolaryngology, Volume 59, pages 289 to 293, 1987). Specifically, 1 mL of a bacterial suspension of staphylococcus aureus clinical isolate (10^8 CFU/mL) was continuously injected into both maxillary sinuses of the rabbits once a day for 3 days, to induce acute sinusitis. From the day after the bacterial injection of the third day, a homemade nose nozzle was inserted into both sinuses of the rabbits, and a solution dissolved using a base (glycerin 2.6 w/v %, sodium edetate 0.01 w/v %, benzalkonium chloride 0.002 w/v %, a suitable volume of sterilized purified water, and sodium hydroxide were used to adjust to pH 5.5) to achieve lomefloxacin hydrochloride of 0.1, 0.3, and 0.5 w/v % was atomized for inhalation continuously for 7 days for 5 minutes at a time using 2 mL twice a day using an ultrasonic inhaler (NE-U11B,

OMRON Corp.). After killing the rabbits under anesthesia the day after ending the drug dosing, the maxillary sinus was extricated and a Seed Swab (Eiken Industries Co., Ltd.) was used to sample the secretions on the mucous membrane, a bacteria test was performed with this as a bacterial test sample, and the positive rate was calculated. A judgment was also made according to the grading criterion noted below on the volume of residual fluid in the maxillary sinus and on the state of the mucous membrane. Note that a saline solution atomization inhalation was performed in the same manner on a control group.

[0019] Criterion for Grading the State of the Pooled Fluid and Mucous Membrane Within the Maxillary Sinus

1. Pooled Fluid

Findings	Points
None	0
Slight amount of pooled fluid in sinus found	1.0
Purulent pooled fluid found in 1/4 of maxillary sinus	2.0
Purulent pooled fluid found in 1/2 of maxillary sinus	3.0
Purulent pooled fluid found in more than 3/4 of maxillary sinus	4.0

2. Mucous Membrane Color Tone

Color Tone	Points
Normal	0
Slightly Red	0.5
Red	1.0
Dark Red	2.0
Pale	3.0

3. Mucous Membrane Swelling

Findings	Points
None	0
Slight amount of swelling found	0.5
Light swelling found	1.0
Clear swelling found to occupy 1/4 of maxillary sinus	2.0
Clear swelling found to occupy 1/2 of maxillary sinus	3.0
Clear swelling found to occupy more than 3/4 of maxillary sinus	4.0

[0020] (Experiment Results) As shown in table 1, atomization inhalation of lomefloxacin was effective on acute sinusitis in rabbits.

[0021]

[Table 1]

Pharmacological Agent	Number of Examples	Germ Test Positive Rate (%)	Condition in Maxillary Sinus		
			Pooled Fluid	Mucous Membrane Color Tone	Mucous Membrane Swelling
Saline Solution	6	66.7	1.5 ± 0.3	1.8 ± 0.6	1.2 ± 0.2
0.1 w/v % Lomefloxacin	8	50.0	1.3 ± 0.3	0.6 ± 0.1	0.7 ± 0.1
0.3 w/v % Lomefloxacin	10	60.0	1.0 ± 0.0	0.6 ± 0.1	0.5 ± 0.0*
0.5 w/v % Lomefloxacin	10	40.0	0.6 ±0.2	0.6 ± 0.1	0.4 ± 0.1 **

Values indicate the average value ± the standard deviation.

*: Indicates that there is a significant difference when there is a significance level of less than 0.05 % in relation to the saline solution dosing group.

**: Indicates there is a significant difference when there is a significance level of less than [illegible; text covered over in copy] % in relation to the saline solution dosing group.

[0022] (Test Example 4) Migration Test of Lomefloxacin [illegible; text covered over in copy]

(Experimental Method) A Japanese white male rabbit was retained in a retention container, and underwent atomization inhalation with an ultrasonic inhaler (NE-U11B, OMRON Corp.) for 5 minutes once a day using 2 mL of the composition of working example 2 to be described later. Rabbits were killed at 15 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours after atomization inhalation, the nasal cavity was extricated, and the mucous membranes of the left and right maxillary sinus were collected. Blood was collected from the ear vein over a period of time, and serum was isolated after centrifuging. The lomefloxacin in the collected mucous membranes and serum was measured by HPLC.

[0023] (Experiment Results) Table 2 shows the transition in tissue concentration of the lomefloxacin in the maxillary sinus mucous membranes and serum.

[0024]

[Table 2]

Time	Lomefloxacin Migration Volume	
	Maxillary Sinus (μg/g tissue concentration volume)	Serum (μg/mL)
After 15 minutes	12.69 ± 7.61	0.047 ± 0.019
After 30 minutes	3.93 ± 1.52	0.075 ± 0.024
After 1 hour	1.69 ± 0.37	0.062 ± 0.020
After 2 hours	1.11 ± 0.48	0.051 ± 0.018
After 4 hours	0.74 ± 0.21	0.033 ± 0.020 [a)]

Values indicate the average value ± the standard deviation. (The example count was 5 examples each, but a) was 3 examples.)

[0025] Lomefloxacin migrates in high concentration to the maxillary sinus mucous membranes which are the target site, but there is only slight migration to the serum, and we found that it can be used safely without having a systemic effect.

[0026] (Test Example 5) Lomefloxacin Toxicity Test When Used With a Nebulizer

2 mL of the composition of working example 2 to be described later was used in an ultrasonic inhaler (NE-U11B, OMRON Corp.) on rabbits, and inhalation was continued for 42 days for 5 minutes once a day, and when we studied toxicity, there were no cases of death during the period the nebulizer was used, and no abnormalities were found in the general condition, weight, food consumption, macroscopic observation of each organ, or wet weight of the organs. Also, with the histopathological evaluation of the respiratory organs (middle meatus, paranasal sinuses (maxillary sinus), pharynx (including the tonsils), laryngopharynx, trachea, lungs, and tracheal lymph nodes), there was a finding of slight cell wetness into the lung lymph nodes and into the pulmonary alveoli, but the same findings were acknowledged for the saline solution dosing group, so there was no difference. Specifically, it was judged that there was no irritation or toxicity even when lomefloxacin hydrochloride was used for 6 weeks in the form of nebulizer therapy.

[0027] (Test Example 6) Lomefloxacin Ototoxicity Test

0.2 mL of the composition of working example 2 to be described later was injected once in the middle ear of the left ear of a marmot, and this was done twice each day at 8 hour intervals for 14 days, and we studied the effect on the ear tissues, but no difference was found in the left and right ear for the auditory brainstem response threshold in terms of acoustic sensory function, and histopathologically as well, no abnormalities were found in the vestibular organs, cochlear canal, or middle ear mucous membranes, so it was determined that lomefloxacin is not ototoxic.

[0028] (Working Examples)

Working Example 1: The formula below was mixed, pH was adjusted to 6.5 using sodium hydroxide, and this was used as a composition for nebulizers.

Lomefloxacin hydrochloride	0.3 g
Sodium hydroxide	Suitable amount

Saline solution	Total volume 100 mL

[0029]

Working Example 2: The formula noted below was mixed, pH was adjusted to 5.5 using sodium hydroxide, and this was used as a composition for nebulizers.

Lomefloxacin hydrochloride	0.5 g
Glycerin	2.6 g
Sodium edetate	0.01 g
Benzalkonium chloride	0.002 g
Sodium hydroxide	Suitable amount
Saline solution	Total volume 100 mL (pH 5.5)

[0030]

Working Example 3: The glycerin in the formula of working example 2 was substituted with mannitol (5.1 g), propylene glycol (2.0 g), D-sorbitol (5.48 g), or glucose (5.51 g), and a composition for nebulizers was prepared.

[0031]

[Merits of the Invention] The lomefloxacin and salt thereof used with the present invention has a broad antibacterial action, has low antigenicity, and is not found to be ototoxic, and is also stable as a liquid solution and can be made into an even mist, and furthermore is not affected by ultrasonic waves, so it can be safely and effectively used for nebulizer therapy for treating acute and chronic infections of the nasal/paranasal sinuses and laryngopharynx.